Our results point to KCa1.1 channels as a promising new target for RA therapy and open the possibility for treatments that would not induce immunosuppression.

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The Functional Swtich in Potassium Channels in Myotonic Dystrophy Type 1 Impairs Proliferation, Migration and Fusion During Myogenesis

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Voltage-gated K^+ channels (Kv) are responsible for myoblasts proliferation and differentiation by triggering changes in membrane potential and cell volume. Since individuals with myotonic dystrophy type 1 (DM1) display reduced myogenesis led by prolonged myoblasts proliferation and delayed myotubes fusion, we investigated the roles of K^+ channels in primary human myoblasts obtained from DM1 patients and healthy volunteers. DM1 is an autosomal dominant neuromuscular disorder affecting 1 in 8000 people worldwide. It is the most common adult-onset muscular dystrophy and currently has no treatment. DM1 is characterized by muscle wasting and multi-system disorders.

We have identified a switch in functional potassium channel expression from KCa1.1 to Kv1 channels when comparing myoblasts from healthy individuals to myoblasts from patients with DM1. We showed increase in Kv1.2 and Kv1.5 channels, and decrease in KCa1.1 channels in DM1 myoblasts at mRNA level by RT-PCR, at protein level by immunofluorescence, and at channel activity by patch-clamp technique. We hypothesized that this switch in K^+ channels plays a role in the reduced myogenesis observed in patients with DM1, and that selective inhibition of Kv1 channels rescues the pathological features of DM1 in skeletal muscle.

We show that pharmacological inhibition of Kv1 channels in DM1 myoblasts normalized proliferation, rescued matrix metalloproteinase-2 (MMP-2, a protease necessary for myotube fusion) production, and partially rescued myotube fusion shown as increase in fusion index. On the contrary, selective inhibition of KCa1.1 in normal myoblasts lowered MMP-2 production, impaired wound healing repair, and decreased myotubes formation. Therefore we conclude that loss of KCa1.1 and up-regulation of Kv1 channels in DM1 impairs early stage of myogenesis and can be partially rescued by modulating such K^+ channels.

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Altered Gating of Kv1.3 Channels of T Lymphocytes in Smith-Lemli-Opitz Syndrome

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The Smith-Lemli-Opitz syndrome (SLO) is a multiple congenital anomaly, caused by a decreased or abolished activity of 7-dehydrocholesterol (7DHC) reductase, which results in the accumulation of the cholesterol precursor 7DHC in the serum and potentially in the cell membrane as well. Increased 7DHC/cholesterol ratio may modify the physico-chemical properties of plasma membrane, and hence may influence the operation of the ion channels in many cell types including T cells. To test this hypothesis we compared the biophysical properties of Kv1.3 channels in T cells of SLO patients (SLO-T-cells), T-cells of healthy volunteers loaded with 7DHC (7DHC-T-cells) and control T cells. The physiological consequence of altered Kv1.3 gating was measured by the proliferative capacity of $CD3^+$ lymphocytes.

T lymphocytes were isolated from the peripheral blood of healthy volunteers (age-matched controls) and patients with SLO. 7DHC elevation in T lymphocytes membrane was achieved upon treatment with cyclodextrin/7DHC complex. Kv1.3 currents were measured using whole-cell patch-clamp. Proliferation rate of lymphocytes was assessed with CFSE-dilution assay upon anti-CD3/anti-CD28 stimulation.

Our results showed that both activation and inactivation kinetics were significantly slower, and the midpoint of the steady-state activation was shifted toward positive voltages in the SLO-T-cells compared to control ($tau_{a,SLO}$: 0.72 ms, $tau_{a,c}$: 0.60 ms ; $tau_{i,SLO}$: 238,48 ms, $tau_{i,c}$: 213,19 ms; $V_{1/2,SLO}$: - 21.762 mV ,$V_{1/2,c}$: - 27.98 mV). Qualitatively and quantitatively differences in the gating of Kv1.3 channels were observed in 7DHC-T-cells vs. control. T-cells from SLO patients had decreased proliferation rate as compared to healthy controls. These data demonstrate that elevated 7DHC level of cell membrane can modify the operation of ion channels and may contribute to the neurodegenerative defects in SLO. (Mecenatura OSTRAT/260/2012, TÁMOP 4.2.4.A/2-11-1-2012-0001).

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Localization of the *Plasmodium Falciparum* K^+ Channel, Pfkch1

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The causative agent of malaria is the unicellular protozoan Plasmodium. The parasite has a complex life cycle, involving asexual replication in human red blood cells (RBCs) as well as sexual replication, forming egg-like cells called oocysts in the mosquito vector. In endemic areas it is estimated that 250 million people get infected with malaria annually, resulting in 500.000-1.000.000 deaths. Increasing resistance towards known antimalarial drugs poses a significant problem in the fight against malaria. Therefore, the development of novel drugs that target vital proteins encoded by the parasite has attracted major attention. Plasmodium falciparum, the species responsible for the majority of malaria- associated fatalities, encodes two putative K^+ channels, PfKch1 and PfKch2, which have been cloned in our laboratories. Although viable in all intraerythrocytic stages, Kch1-null P. berghei parasites exhibit a total inhibition of oocyst development in the mosquito midgut. Thus, Kch1 might serve as a potential target in novel parasite transmission-blocking strategies. However, earlier published immunofluorescence microscopy images have suggested that Kch1 is located in the infected human red blood cell membrane. In the present study, polyclonal antibodies were raised against the PfKch1 channel and our results demonstrate that Kch1 is located in the parasites plasma membrane in all blood stages of malaria. This finding is in accordance with functional data previously published from our lab. Thus, Kch1 may be a major K^+ transporter in the parasite plasma membrane and play an important role for regulation of the membrane potential of the Plasmodium parasite.

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Malignant Lymphoblasts in T Cell Acute Lymphoblastic Leukemia Express High Levels of Kv1.3

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Acute lymploblastic leukemia (ALL) is the most common malignancy in childhood and young adolescence, comprising about 30% of all cancers. Despite the fact that treatment strategies have strongly improved in the last decades, ALL is still one of the major causes of cancer-related death in children. Whilst the subtypes of ALL deriving from B cells are already well described by their genetic and molecular features, the biology of the T cell-linage (T-ALL) is very heterogeneous and with the exception of some frequently occurring genetic aberrations until now poorly understood.

By controlling the membrane potential, K^+ channels regulate Ca^{2+} signaling and subsequent proliferation in human lymphocytes. Expression levels of the two major K^+ channels found in lymphocytes (Kv1.3 and KCa3.1) are subtype-specific. The more abundantly expressed channel typically dominates the Ca^{2+} signaling events that result in proliferation. This renders the cells sensitive to specific blockade of this more highly expressed K^+ channel. We investigated lymph node and bone marrow samples of T-ALL patients and found high expression levels of Kv1.3 channels in malignant T-lymphoblasts, confirmed by immunohistochemistry and immunofluorescence microscopy. Moreover, we also detected high Kv1.3 currents in a T-ALL cell line (Molt-4) compared to low KCa.3.1 currents, which was confirmed by mRNA data, as well as fluorescence microscopy. The functional role of Kv1.3 in proliferation of malignant T-lymphoblasts was elucidated by the pharmacological blockade of Kv1.3. Proliferation rates were significantly diminished by treatment with PAP-1 and ShK-L5 (specific blockers for Kv1.3 channels) but not by TRAM-34 or ICA-17043 (specific blockers for KCa3.1). Further investigation might thus suggest a role for Kv1.3 channels in the treatment of T-ALL. Supported by RO1 GM076063 from the National Institute of Health and the Austrian National Bank Jubilaeumsfons No. 14311.

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Margatoxin is a Nonselective Inhibitor of Kv1.3 Channels - A Comprehensive Study

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Ion channel inhibitor peptide toxins have become lead compounds for potential therapeutic use in the last decade. In the case of Kv1.3, the voltage-gated K^+